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Plasma HIV viral load and C-reactive protein as predictors of HIV disease progression among HIV-infected children

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Background: Biomarkers that predict the rate of HIV disease progression in HIV-infected children might assist in clinical decisions of when to start ARV among children with mild to moderate immune suppression.

Methods: This is a substudy of the PREDICT study, a randomized trial of immediate versus deferred antiretroviral initiation in children aged 1-12 years in Thailand and Cambodia. HIV-infected children with CD4 15-24% had CD4 monitoring every 12 weeks and started ART when CD4 < 15%. Long term non progressors (LTNP) were defined as age > 8 years anytime during the study with CD4 > 15%, slow progressors were <8 years with CD4 > 15% at the study end, and routine progressors had CD4 decline to <15% before age 8 years. Baseline HIV RNA, soluble CD14 (sCD14) and C-reactive protein (CRP) were measured and multinomial logistic regression was performed to discern relative risk (RR) ratios of disease progression for each biomarker with LTNP as a reference group.

Results: There were 147 HIV-infected children with mean age of 6.5 years, %CD4 of 20.6, plasma HIV RNA of 4.6 log10 copies/ml. There were 85,25 and,37 children in LTNP, slow and routine progressor groups, respectively. In multivariate models, the RR (95%CI) of being a slow progressor for children with baseline viral load ≥ 5 log10 copies/ml was 6.0 (1.9-18.6; p = 0.002) after adjusting for sCD14 and CRP. The RR (95% CI) of being a routine progressor for children with baseline viral load ≥ 5 log10 copies/ml was 25.2 (8.1 – 77.7; p <0.0001) and 5.1 (1.6 – 16.0; p = 0.006) in those with CRP ≥ 3 mg/L after adjusting for sCD14. Although mean (SD) sCD14 was significantly higher in the routine progressors versus the LTNP (1.96 (0.43) vs 1.66(0.38) million pg/mL; P < 0.001), it was not significant in a multivariate model after adjusting for viral load and CRP.

Conclusion: Baseline HIV RNA ≥ 5 log and CRP ≥ 3 mg/L are independent predictors of faster HIV disease progression rates. HIV RNA with/without CRP could aid in deciding which children should start ARV sooner.

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Susceptibility of HIV-1 CRF01_AE viruses to a CD4-binding site monoclonal antibody, IgG1 b12

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Background: A human monoclonal antibody, IgG1 b12 (b12) recognizes a conformational epitope on human immunodeficiency virus type 1 (HIV-1) envelope glycoprotein (Env) gp120 that overlaps the CD4 binding site. Although b12 is able to broadly neutralize HIV-1 subtype B, C and D viruses, it poorly neutralizes most CRF01_AE viruses. In this report, we examined the mechanisms underlying low b12 susceptibility of CRF01_AE viruses, using recently established CRF01_AE Env (AE-Env)-recombinant viruses.

Methods: AE-Env genes were cloned into the pNL4-3-derived luciferase reporter proviral construct, pNL-envCT to generate AE-Env-recombinant viruses. In addition, N-linked glycosylation mutants were generated by site-directed mutagenesis. Viral supernatants were prepared by transfecting 293T cells with the proviral construct. Then, neutralization susceptibility of the recombinant viruses to b12 was examined.

Results: We found that two potential N-linked glycosylation (PNLG) sites, designated as N186 and N197 (amino acid numbering is based on HXB2 Env), in the V2 and C2 region of Env gp120 played an important role in regulating the b12 susceptibility of AE-Env-recombinant viruses. Namely, removal of N186 and/or N197 conferred the b12 susceptibility of 15 resistant AE-Env-recombinant viruses, whereas the removal of N301, N339, N386 or N392 from the remaining b12-resistant viruses from which N186 and/or N197 had been removed was not sufficient to confer the b12 susceptibility. Interestingly, the introduction of an aspartic acid at residue 185 into a resistant virus from which N197 had been removed, 47CC11-N197Q-G185D, conferred the b12 susceptibility. In addition, the introduction of D185 into this virus from which N197 was not removed, 47CC11-G185D, also increased the b12 susceptibility, although the extent of b12 susceptibility was lower than that of 47CC11-N197Q-G185D. The conservation of D185 in Subtype B, C and CRF01_AE which obtained from the HIV sequence

database (n = 200) were 74%, 19.5% and 24.5%. Further studies to clarify the mechanism underlying the b12 resistance of CRF01_AE viruses are ongoing.

Conclusion: Neutralization susceptibility of AE-Env is regulated by the N-linked glycosylation sites, N186 and N197, in V2 and C2 regions cooperated with amino acid residue 185 in V2 region of gp120.

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In search for a new anti-HIV-1 drug through inhibition of CA-CypA interaction

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Background: Currently available antiretroviral drugs are classified into 4 classes including reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors and entry/fusion inhibitors. Highly active antiretroviral therapy (HAART), using a combination of three or more antiretroviral drugs, can manage HIV-1 replication for many years; however, the virus tries to survive under antiretroviral therapy by mutate itself to become a drug-resistant variant. Therefore, the development of new classes of anti-HIV-1 drugs with different inhibition mechanisms is required. The interaction between HIV-1 capsid protein (CA) and human cyclophilin A (CypA) is crucial for HIV-1 life cycle. Although the role of CypA in HIV-1 life cycle remains unclear, CA-CypA interaction is an interesting target for the development of new anti-HIV-1 agents.

Methods: Seventy-seven compounds which could bind to CA *in silico* were tested for its activity against HIV-1 replication. Each compound was tested *in vitro* at a fix concentration using a vesicular stomatitis virus G protein (VSVG)-pseudotyped, luciferase reporter HIV-1 in the 1st round screening. The compounds that showed potent HIV-1 inhibition were evaluated for dose-dependent effect and cytotoxicity effect in the 2ndround screening.

Results: Eleven compounds showed a potent inhibitory effect on HIV-1 replication in the 1st round screening. Five compounds were considered to be safe and potent HIV-1 inhibitors in the 2nd round screening.

Conclusion: Although most compounds had little or no effect on HIV-1 replication, five compounds showed a potent inhibitory activity on viral replication through our screening. Further studies on their inhibitory mechanisms are underway.

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HCV co-infection may promote the subclinical left ventricular dysfunction development in HIV-infected subjects

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Background: Chronic HCV infection may be linked with possible myocarditis and cardiomyopathy development. The pathophysiology of cardiac injury in hepatitis C is still unknown, however it seems that inflammation and apoptosis may play a crucial role in this progressive process. The brain natriuretic peptide (BNP) is a hormone secreted predominantly from the cardiac ventricles on response to increased wall stress, wall distension and stretching or neurohormonal activation. Presently, BNP is commonly used as a sensitive biomarker of subclinical/clinical left ventricular (LV) dysfunction.

The present study aimed to compare BNP serum levels in HIV-infected and HCV/HIV co-infected subjects with or without ARV therapy.

Methods: Eighty HIV-infected patients (65 males, 15 females, mean age 40 years; 29 with HCV co-infection, 48 on cART) were included to the cross-sectional study. Compensated liver cirrhosis was diagnosed clinically in 9 (11%) studied subjects, all of them had HCV/HIV co-infection. One HCV/HIV co-infected subject had confirmed right ventricular dysfunction diagnosis. The BNP serum levels were evaluated by ELISA. A BNP cut-off level for heart failure diagnosis was 100 pg/mL as in immunocompetent population. In statistical analyses U Mann-Whitney, Spearman correlation and chi2 tests were used. $P < 0.05$ was considered statistically significant.

Results: Seventy eight (97.5%) studied subjects had BNP concentration above 42 fmol/L (100 pg/mL), 7 patients (8.7%) had concentration above 168 fmol/L (400 pg/mL) which is associated with a worse outcome. There was no difference in mean BNP serum levels in ARV-treated and untreated patients (106.2 ± 94.5 vs 116.4 ± 87.9 fmol/L; $p = 0.15$). However, the mean BNP serum level was significantly higher in HCV/HIV co-infected in comparison to HIV mono-infected patients (160.0 ± 130.9 vs 81.9 ± 37.2 fmol/L; $p < 0.0001$). There was no relationship between BNP serum levels and HIV viral load, CD4 cell count, gender and ABC or PIs use.

Conclusion: HCV co-infection may significantly enhance the risk of the subclinical LV dysfunction in HIV-infected subjects. The ARV therapy probably does not reduce progressive myocardial damage in this group of patients. We suggest regular BNP screening in every HCV/HIV co-infected patient. Every LV dysfunction suspicion should be confirmed by echocardiographic.

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